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Biochemical Dysregulation of Pre-Eclampsia and Gestational Diabetes Mellitus

Maria Portelli and Byron Baron

Abstract

Emerging evidence indicates that among the various pregnancy complications, pre-eclampsia and gestational diabetes mellitus (GDM) seem to have, at least in part, shared underlying etiologies. Apart from sharing numerous risk factors, it has been shown that the rate of pre-eclampsia is influenced by the presence and severity of GDM, with hyperglycemia due to insulin resistance and the biochemical changes this brings about (angiogenic imbalance, oxidative stress and inflammation), playing some role in the pathogenesis of endothelial dysfunction leading to the development of pre-eclampsia. However, so far the biochemical mechanisms underlying and linking these two conditions is still not properly understood. The altered physiological parameters, dysregulation of potential protein biomarkers and DNA-related changes (mutations, methylations, miRNAs) will be combined in this review to explore possible underlying mechanisms.

Keywords: pre-eclampsia, gestational diabetes mellitus, endothelial dysfunction, insulin resistance, angiogenic factors, oxidative stress, inflammation

Key points

- A combination of maternal risk factors appears to contribute to the similar biochemical dysregulation present in both pre-eclampsia and GDM.
- The common biochemical characteristics underlying these conditions include endothelial dysfunction, angiogenic imbalance, insulin resistance, oxidative stress, inflammation and dyslipidemia.
- Detailed evaluation of pre-pregnancy characteristics and clearer distinction between the different disease statuses is required to better understand the shared and separate biochemical pathways.

1. Pathophysiology of pre-eclampsia and gestational diabetes mellitus

Pre-eclampsia is a multisystem, pregnancy-specific disorder, presenting new-onset hypertension and proteinuria after 20 weeks of gestation. It is a leading cause of maternal and foetal morbidity and mortality, with delivery being the only known

cure. Pre-eclampsia complicates 2–5% of pregnancies in Europe and America and can reach up to 10% of pregnancies in developing countries [1].

Pre-eclampsia is characterised by a first, asymptomatic stage involving impaired trophoblastic penetration of the decidua (both into the superficial myometrium at 14–16 weeks and into the deep myometrium at 18–20 weeks), limiting the remodeling of the maternal uterine spiral arteries for uteroplacental blood perfusion and producing local placental hypoxia and oxidative stress, which consequently leads to insufficient blood perfusion, inflammation, apoptosis, and structural damage. In the second stage, placental factors released into the maternal circulation from the poorly perfused placenta, together with the aberrant expression of pro-inflammatory, anti-angiogenic, and angiogenic factors, eventually cause the endothelial dysfunction that leads to the main clinical symptoms of pre-eclampsia [1].

This disorder can have an early onset (before 34 weeks of gestation) or a late onset (after 34 weeks of gestation), with the placentas of women with early onset pre-eclampsia presenting hypoplasia (small placental size) and a significantly higher number of placental vascular lesions compared to those with late onset PE, which present hyperplasia (increased placental size) and histological evidence of placental inflammation, with absence of vascular insufficiency, suggesting that pre-eclampsia might be more than a single condition [2].

Gestational diabetes mellitus (GDM) is defined as hyperglycemia that is first diagnosed during pregnancy. This definition of GDM does not preclude the possible existence of unrecognised pre-pregnancy diabetes. The prevalence of GDM ranges from 2 to 10% of all pregnancies in developed countries [3] and is associated with birth complications, including macrosomia and operative delivery. GDM develops from a dysfunction of the pancreatic Beta cells such that the insulin supply is inadequate to meet tissue demands for normal blood glucose regulation. This insulin resistance leads to increased levels of glucose production and free fatty acids, with subsequent increased blood glucose levels [4].

All forms of diabetes (GDM, type 1 diabetes - T1D and type 2 diabetes mellitus - T2DM) increase the risk of pre-eclampsia, with GDM being an independent risk factor for the development of pre-eclampsia [5, 6], and pre-existing diabetes being a risk factor for both early- and late-onset pre-eclampsia [7]. The incidence of pre-eclampsia increases from 2–7% of pregnancies in non-diabetic women to 15–20% in women with T1D and 10–14% in women with T2DM [8].

Pre-eclampsia and GDM share a number of risk factors, including advanced maternal age, nulliparity, multifetal pregnancies, non-white ethnicity, and pre-pregnancy obesity [5, 9]. Both pre-eclampsia and GDM also have long-term health implications, with pre-eclampsia increasing the risk of future cardiovascular disease, stroke, kidney disease, ophthalmic disease and development of T2DM (even without GDM), while GDM increases the risk of cardiovascular disease and T2DM for both mother and child [8].

Although the exact pathophysiology is still unknown, it would seem that a combination of maternal risk factors contribute to the similar biochemical dysregulation present in both pre-eclampsia and GDM, compared to healthy pregnancies, including endothelial dysfunction, angiogenic imbalance, insulin resistance, oxidative stress, inflammation and dyslipidemia [8] suggests shared etiological pathways underlying these conditions. Such biochemical changes might result from a common aetiology, have a common trigger (such as insulin resistance during pregnancy [10]) or be similar responses to different underlying disease processes that existed prior to pregnancy [11]. Similarly, genetic and/or environmental factors that contribute to pre-eclampsia could also increase the risk of diabetic complications later in life or it could be just as possible that pre-eclampsia causes lasting damage that leads to diabetic complications years after pregnancy [8].

2. Endothelial dysfunction

Within the placenta, limited remodelling of the maternal uterine spiral arteries may cause hypoxia [12] or repeated ischemia–reperfusion injury [13], such that the damaged placenta then releases factors into the maternal circulation that contribute to vascular dysfunction [12]. These include the anti-angiogenic proteins soluble vascular endothelial growth factor receptor 1 (sVEGFR-1; or more commonly known as soluble fms-like tyrosine kinase 1 - sFlt-1) and soluble endoglin (sEng) [14, 15]. Excess of these anti-angiogenic proteins contributes to systemic maternal endothelial dysfunction in women with pre-eclampsia [16].

The sFlt-1 protein is a truncated form of VEGF receptor 1, composed of six immunoglobulin-like domains from the ligand-binding, extracellular domain [1]. Once secreted, sFlt-1 binds to the pro-angiogenic ligands vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), acting as a non-signalling decoy, reducing their bio-availability and enhancing endothelial dysfunction [16–18].

The sEng protein is composed of the extracellular domain of Endoglin, following proteolytic cleavage by metalloproteinase (MMP)-14. It binds to Transforming Growth Factor- β 1 (TGF- β 1), inhibiting binding to Endoglin (a TGF- β 1 co-receptor), preventing the activation of endothelial Nitric Oxide Synthase (NOS) and subsequent vasodilation [15].

The levels of sFlt-1 and sEng were found to be proportional to the severity of pre-eclampsia [19–21], with maternal plasma concentrations of sFlt-1 and sEng increasing before pre-eclampsia was diagnosed, making them potential biomarkers for the disease [1, 22–29]. Concomitantly, the increase of sFlt-1 brings about a decrease in maternal plasma concentration of PlGF [18, 30–32]. However, the relative change in sFlt1 and sEng concentrations between two consecutive visits (first and second trimester) seems more useful as a predictive marker for developing pre-eclampsia among both low- and high-risk women than the absolute concentrations [30, 33].

The relationship between anti-angiogenic factors and pre-eclampsia in women with GDM has been explored only in a handful of studies. Women with GDM were found to have higher serum sFlt-1, Placental Protein 13 (PP13), Pentraxin 3 (PTX3), myostatin and follistatin levels early in the second trimester, with sFlt-1 and PTX3 having potential predictive value [34]. Quantitative proteomics of syncytiotrophoblasts from women with GDM and pre-eclampsia identified 11 upregulated and 12 downregulated proteins including increased Flt-1 [35]. Moreover, high sEng, high sFlt-1, low PlGF and high sFlt-1/PlGF ratio increased the odds of developing pre-eclampsia among women with pre-existing diabetes [30].

Further vascular dysfunction results from the inhibition of NOS. Asymmetric dimethylarginine (ADMA) is an analogue of L-arginine and endogenous competitive inhibitor of NOS, resulting in reduced NO synthesis from L-arginine and higher superoxide generation. NO is important in maintaining endothelial homeostasis and elevated ADMA levels are associated with inflammation, insulin resistance, dyslipidemia, obesity, and cardiovascular disease. Numerous studies have measured ADMA levels in women with pre-eclampsia and normotensive women but discrepant findings have been observed. Nevertheless, some reported elevated ADMA levels prior to the development of clinical symptoms of PE, which suggests that ADMA may contribute to the pathophysiology of pre-eclampsia [1, 29].

Poor placentation, oxidative stress, endothelial cell dysfunction and altered glucose metabolism among others generate Damage-Associated Molecular Patterns (DAMPs) including Heat Shock Proteins (HSPs), TNF- α , fetal DNA, hyaluronan, oxidised low-density lipoprotein (LDL) and long pentraxin-3 [36]. HSP70 (and its post-translational modifications) has been shown to be elevated in the placentas and sera of women with PE, reflecting systemic inflammation and oxidative stress, with

HSP70 initially protecting against placental oxidative stress but its overexpression may lead to intervillous endothelial dysfunction and may play a role in the pathogenesis of pre-eclampsia [1, 29]. TLR-4 protein expression, which recognises such DAMPs at the feto-maternal interface, is increased in women with pre-eclampsia [37].

3. Insulin resistance

Insulin resistance or hyperinsulinemia is an impaired response to insulin, characteristic of normal pregnancy, which results in increased insulin secretion by the pancreatic β -cells or relative insulin deficiency due to the pancreatic β -cell deterioration. Insulin resistance is due to an overall decreased expression of the insulin receptor substrate (IRS)-1/2 protein, decreased IRS-1/2 tyrosine phosphorylation and increased IRS-1/2 serine phosphorylation, resulting in reduced glucose transport activity, which was found to be even more pronounced in women with pre-eclampsia and GDM, which might also underlie the future risk for developing T2DM [38].

Insulin resistance via the inhibition of IRS1/2 results in impaired activation of the phosphoinositide 3-kinase (PI3K) and Akt strain transforming (Akt)-dependent signalling pathway, and increased activity of the mammalian target of rapamycin (mTOR) resulting from lower activity of the mitogen activated protein kinase (MAPK) pathway. The reduced Akt activity leads to a decreased production of nitric oxide (NO) (a vasodilator) and increase of endothelin (ET)-1 (a vasoconstrictor) [39], linking endothelial dysfunction and increased risk of pre-eclampsia with GDM.

Compared to normotensive women, women who develop pre-eclampsia are more insulin resistant prior to pregnancy [40], in the first and second trimesters [41], and years after pregnancy [42], and in fact a number of pre-eclampsia risk factors are also associated with insulin resistance [40, 41]. The same was found in women that developed GDM, presenting chronic insulin resistance and chronic β -cell function prior to pregnancy [4, 43]. Women with GDM are then unable to increase insulin production to compensate for the increased insulin resistance and destruction, as happens in normal pregnancy [44]. The metabolic changes observed in GDM are the same as those found in the pre-diabetic stages of T2DM, where pre-diabetes may include patients with metabolic syndrome, GDM, and impaired glucose tolerance.

4. Oxidative stress and mitochondrial dysfunction

During normal pregnancy generation of reactive oxygen species (ROS) is known to be increased and necessary for proper physiology [45]. However, both pre-eclampsia and GDM present a reduced antioxidant status when compared to normal pregnancies, with increased levels of protein and lipid oxidation products [46]. Free radicals react with nucleic acids, proteins and lipids, bring about post-translational modification of proteins [47] and cause structural and functional damage [46]. The changes in a wide variety of oxidative stress metabolites (such as NO, superoxide and peroxynitrite) as well as antioxidant enzymes and compounds (such as catalase, superoxide dismutase (SOD) and vitamin E) have been analysed in relation to pre-eclampsia and GDM compared to normal pregnancies but there is still no consensus since their levels were found to be variable (the same, higher or lower) depending on the cohort studied [48–50]. Although supplementation with antioxidants such as vitamin C, vitamin E or n-acetylcysteine have been found to be ineffective in reducing the risk of pre-eclampsia, calcium and vitamin D supplementation could lower risk of pre-eclampsia [50, 51].

In the case of hyperglycemia, it is known to stimulate ROS production by four major sources, namely glucose auto-oxidation, mitochondrial superoxide

production, endothelial NOS uncoupling and advanced glycation end product (AGE)-dependent NADPH oxidase activation, with glucose auto-oxidation and mitochondrial superoxide likely being the initial contributors to ROS-mediated dysfunction caused by hyperglycemia [52, 53]. Advanced glycation end products are of particular interest as these were found to be able to promote TNF- α mRNA expression and secretion as well as bringing about a significant decrease in eNOS mRNA expression and protein levels via serine phosphorylation [54, 55].

The serum levels of AGEs were higher in women with both early- and late-onset pre-eclampsia and in women with severe pre-eclampsia positively correlated with serum levels of TNF- α and VCAM-1, indicating AGEs are important mediators in regulating the inflammatory pathways of pre-eclampsia [56–58]. Furthermore, treatment with AGEs increased intracellular ROS generation and over-expression of sFlt-1 in an extravillous trophoblast cell line, suggesting that AGEs may be important mediators in the regulation of angiogenic pathways, with accumulation of AGEs possibly contributing to pre-eclampsia by promoting sFlt-1 production via the activation of a RAGE/NADPH oxidase dependent pathway [59].

In women with PE, oxidative markers were significantly higher, while anti-oxidative markers were significantly lower, indicating gradual oxidative damage of the placenta, even before the onset of clinical symptoms [60]. Similarly, women with GDM had higher serum malondialdehyde levels and significantly lower serum glutathione peroxidase activity in the first trimester, with negative correlation in the second and third trimester [61].

Looking directly at the mitochondria, women with early-onset pre-eclampsia showed increased mitochondrial activation, with up-regulation of optic atrophy, type 1 (OPA-1), increased placental mitochondrial DNA copy number, and mitochondrial transcription factor A down-regulation, while both early- and late-onset pre-eclampsia were associated with an elevated phosphate/oxygen ratio [62]. Moreover, a comparative proteomics analysis of placental mitochondria in women with pre-eclampsia compared to healthy pregnancies identified up-regulation of 4 proteins and down-regulation of 22 proteins involved in ROS generation, apoptosis, fatty acid oxidation, respiratory chain function, and the tricarboxylic acid cycle [63].

5. Inflammation

5.1 Cytokines

After ischemia and reperfusion injury, together with oxidative stress, the placenta mounts an inflammatory response releasing cytokines and other inflammatory factors such as Tumour Necrosis Factor- α (TNF- α), Interleukin (IL)-6, and C-reactive protein (CRP), and damaging levels of ROS, which are a characteristic of pre-eclampsia [64] and the altered levels of inflammatory cytokines in both early and late-onset pre-eclampsia correlated with the type of histopathologic changes in the placenta [65].

The proposed mechanism linking insulin resistance and inflammatory pathways involves a reduction in Akt activity, which also reduces NO generation. Reduced Akt activity and reduced plasma level of adiponectin reduce adenosine monophosphate protein kinase (AMPK) activity, such that mTOR activation is facilitated. The increased mTOR-activated signalling and increased extracellular level of leptin and TNF- α result in c-Jun N-terminal kinase (JNK) activation, inhibiting IRS1/2 and reducing insulin signalling. Thus hyperinsulinemia activates a feedback loop of increased vascular inflammation and insulin resistance [39].

In women who later developed GDM, increased leukocyte counts were observed since the first trimester, indicating that inflammation is associated with the

development of GDM [66]. Women with GDM had higher serum levels of TNF- α in the third trimester and TNF- α and IL-6 at term, compared to women with normoglycemia during pregnancy, and TNF- α levels were inversely correlated with insulin sensitivity [67–69]. Moreover, the increase of TNF- α concentration from pregravid to the third trimester was the best predictor of insulin resistance in pregnancy when compared with leptin, cortisol, and other pregnancy-derived hormones independent of fat mass [67]. Years after pregnancy, women with GDM were still found to have higher circulating levels of the inflammatory mediators CRP, Plasminogen Activator Inhibitor-1 (PAI-1), fibrinogen and IL-6, and lower levels of adiponectin, compared to non-diabetic women, increasing the risk for future development of inflammatory-related conditions [70].

5.2 Adipokines

Adipokines (proteins secreted from adipocytes) are involved in a wide range of physiological processes including haemostasis, lipid metabolism, atherosclerosis, blood pressure regulation, insulin sensitivity, angiogenesis, immunity and inflammation, and have been shown to play a role in normal pregnancy [71].

In both pre-eclampsia and GDM, various adipokines are dysregulated, and could be involved in the pathophysiology of these conditions, especially since obesity is a known risk factor for both [72–74]. The most well-studied are adiponectin and leptin. Adiponectin is considered an insulin-sensitising, anti-inflammatory and anti-atherogenic adipokine, which stimulates glucose uptake in skeletal muscle and reduces hepatic glucose production through AMP-activated protein kinase [75]. Leptin plays a key role in the regulation of energy intake and energy expenditure (increasing insulin sensitivity by influencing insulin secretion, glucose utilisation, glycogen synthesis and fatty acid metabolism) and is involved in a number of physiological processes including regulation of gonadotrophin-releasing hormone (GnRH) secretion, inflammation, immune response, reproduction and angiogenesis [76].

Increased concentrations of adiponectin were found in women with pre-eclampsia [77–80], which could be a mechanism to counter the inflammatory response and improve insulin sensitivity and vascular function [81]. Inversely, decreased concentrations of adiponectin, and up-regulated expression of its receptor adiponectin receptor-1 (ADIPOR1), were found in women with GDM [82–85], possibly suppressed by TNF- α , other proinflammatory mediators and insulin [38], which might further aggravate insulin resistance since adiponectin has insulin-sensitising effects. Adiponectin levels during pregnancy were also found to predict postpartum insulin sensitivity and β -cell function, even among non-obese women [86].

High levels of leptin were found both in women with pre-eclampsia [77, 87–89], even before the clinical onset of the disease [90–93] (suggesting a pathophysiological role), and women with GDM [69, 94–96]. In pre-eclampsia pregnancies increased leptin concentrations affect metabolic, immune, and angiogenic responses, regulating placental growth (potentially resulting in placental hypertrophy), stimulating angiogenesis and increased blood supply to the placenta as well as regulating placental nutrient transport, use, and storage of lipids and amino acids, possibly as a compensatory mechanism to increase nutrient delivery to the underperfused placenta [97]. In GDM pregnancies leptin acts as a pro-inflammatory adipokine, being associated with increased production of pro-inflammatory cytokines (IL-6 and TNF- α), stimulating the production of CC-chemokine ligands (CCL3, CCL4 and CCL5), production of ROS and promoting cell proliferation and migratory responses [98].

5.3 Peroxisome proliferator-activated receptors

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that form part of the nuclear hormone receptor

superfamily, that regulate genes involved in metabolic, anti-inflammatory and developmental processes. There are three mammalian types of PPARs namely PPAR α , PPAR β/δ , and PPAR γ . PPARs perform functions throughout pregnancy including implantation, trophoblast differentiation and placental function, and are also involved in embryonic and fetal development. The regulation of metabolic and anti-inflammatory pathways by the PPAR system is considered crucial in the development of GDM [99].

During normal pregnancy, PPAR γ activators such as specific prostanoids or fatty acid derivatives are upregulated in maternal serum [100]. In women with PE, circulating PPAR γ ligands have been shown to be suppressed even before clinical presentation [101]. Animal models have shown that administration of a PPAR γ antagonist early during gestation results in PE-like symptoms (such as elevated blood pressure, proteinuria, endothelial dysfunction, and increased platelet aggregation) [102], while treatment with a PPAR γ agonist improves pregnancy outcome in animals with pre-eclampsia by reducing oxidative stress in a heme oxygenase (HO)-1-dependent pathway [103]. Another study found that while the placentas of women with pre-eclampsia did not present any changes PPAR protein expression or DNA binding activity, those from women with GDM presented decreased PPAR γ and PPAR α protein concentrations and decreased concentrations of RXR α (the heterodimer partner of PPAR γ) [104].

6. Genetic and epigenetic influences

6.1 Genetics

Besides the finding that women having their first baby with a family history of pre-eclampsia increases two- to five-fold the risk of developing PE, the genetic predisposition to pre-eclampsia has been studied to various degrees, with genetic factors possibly playing a role in increased sFlt-1 production and placental size, imprinted genes possibly involved in the maternal contribution to develop pre-eclampsia and a number of genetic disorders being associated with pre-eclampsia (trisomy 13, angiotensinogen gene variant T235, eNOS, genes causing thrombophilia, and a number of SNPs) despite little significance [105]. pre-eclampsia is an extremely complex spectrum disorder with gene clusters falling into four categories, those involved in (i) hormone secretion, response to hypoxia, and response to nutrient levels; (ii) immune and inflammatory responses (including cytokine/interferon signalling); (iii) metabolism, cell proliferation and cell cycle as well as stress response and DNA damage; (iv) hormone secretion and ion channel activity, and nervous system development or neurological system processes [106].

A few studies have looked into the genetics of GDM and its genetic relationship with T2DM with the major genes being *MTNR1B*, *TCF7L2*, *IRS1*, *IGF2BP2*, *TNF- α* and *PPARG* [107, 108]. Genes linked to GDM participate in cell functions involving cell activation, immune response, organ development, and regulation of cell death [109], but do not shed light on the underlying cause of the disorder.

6.2 DNA methylation

The effects of pre-eclampsia and GDM on the intrauterine environment also bring about epigenetic modifications including DNA methylation [110]. Although the placenta is known to be hypomethylated relative to other tissues [111], studies measuring CpG island methylation in the RefSeq genes (i.e. mainly promoter methylation, covering about 1.5% of total genomic CpGs) found a predominance of

hypermethylation at methylation variable positions in the placentas of women with pre-eclampsia or GDM, with dysregulation of metabolic pathways, signalling pathways and immune response pathways [112–120]. When interrogating global placental DNA methylation, a preliminary study showed a negative association between the degree of methylation and both pre-eclampsia and GDM [121]. However, a much larger study later found increased placental global DNA hypermethylation in GDM women, independent of other risk factors [122].

One driver for DNA hypermethylation in the placenta might be oxidative stress, since both pre-eclampsia and GDM are associated with increased oxidative stress and it has been shown in a T2DM rat model that this condition brings about global DNA hypermethylation in the liver, and that DNA hypermethylation can be reduced by polyphenols that act as antioxidants [123–125].

6.3 Regulatory microRNAs

The miRNA expression pattern in the placenta (predominantly in the trophoblast) changes throughout pregnancy due to the involvement of miRNAs in regulating different aspects of trophoblast biology [126]. Such changes are also detectable in the maternal plasma [127, 128].

A number of studies have identified over 100 differentially expressed miRNAs in the placenta or sera of women with pre-eclampsia compared to normotensive controls. Among these are miRNAs involved in cellular proliferation, cellular migration, inflammation, signal transduction, vascular remodelling and mitochondrial function [126, 129–134]. Increased plasma levels of miR-210 were associated with the severity of pre-eclampsia [135].

The studies focusing on miRNAs in the sera of women with GDM are fewer as are the identified miRNAs (around 50 in total). The processes that seem to be mostly targeted by miRNAs in GDM are insulin/IGF1 signalling (IRS-1, IRS-2, SOS-1, MAPK-1, Insig1, PCK2), adipogenesis, endothelial function, inflammation (TGF- β signalling pathway), and energy balance (EGFR/PI3K/Akt/mTOR signalling pathway) [136–139]. Moreover, 9 miRNAs were found to be shared among T1D, T2DM and GDM, with an additional 19 miRNAs specific to GDM, indicating that GDM leads to changes that differ from those of the other forms of diabetes [140]. Interestingly, the histone methyltransferase enhancer of zester homologue 2 isoform beta (EZH2- β) has been linked to GDM via miRNA control [141].

7. Insight from metformin

Metformin (1,1-Dimethylbiguanide) is a small molecule that can readily cross the placental barrier [142]. It is the treatment of choice for GDM due to its efficacy and safety for the unborn child compared to insulin [143]. Metformin acts through the mitochondria, by inhibiting complex I of the electron transport chain, activating AMPK that controls cellular energy homeostasis and thus reduces gluconeogenesis and enhanced insulin suppression of endogenous glucose production by the liver [144].

Metformin was shown to be superior to insulin in reducing the frequency of gestational hypertension and possibly pre-eclampsia [145–147], by reducing ROS production, reducing endothelial dysfunction (by reducing sFlt-1 and sEng secretion regulated through the mitochondria), reducing inflammation (by reducing VCAM-1 mRNA expression induced by TNF- α), enhancing vasodilation and inducing angiogenesis [47, 148]. This suggests that there are similar perturbations in the cellular energy balance of patients with pre-eclampsia and GDM.

8. Conclusions

Much of the biochemical dysregulation that is common to both GDM and pre-eclampsia suggests overlapping pathophysiology (**Figure 1**). However, the available data does not clearly outline a common etiologic pathway, mainly due to limited analysis power to compare the different patient groups. Detailed evaluation of pre-pregnancy characteristics and clearer distinction between the different disease

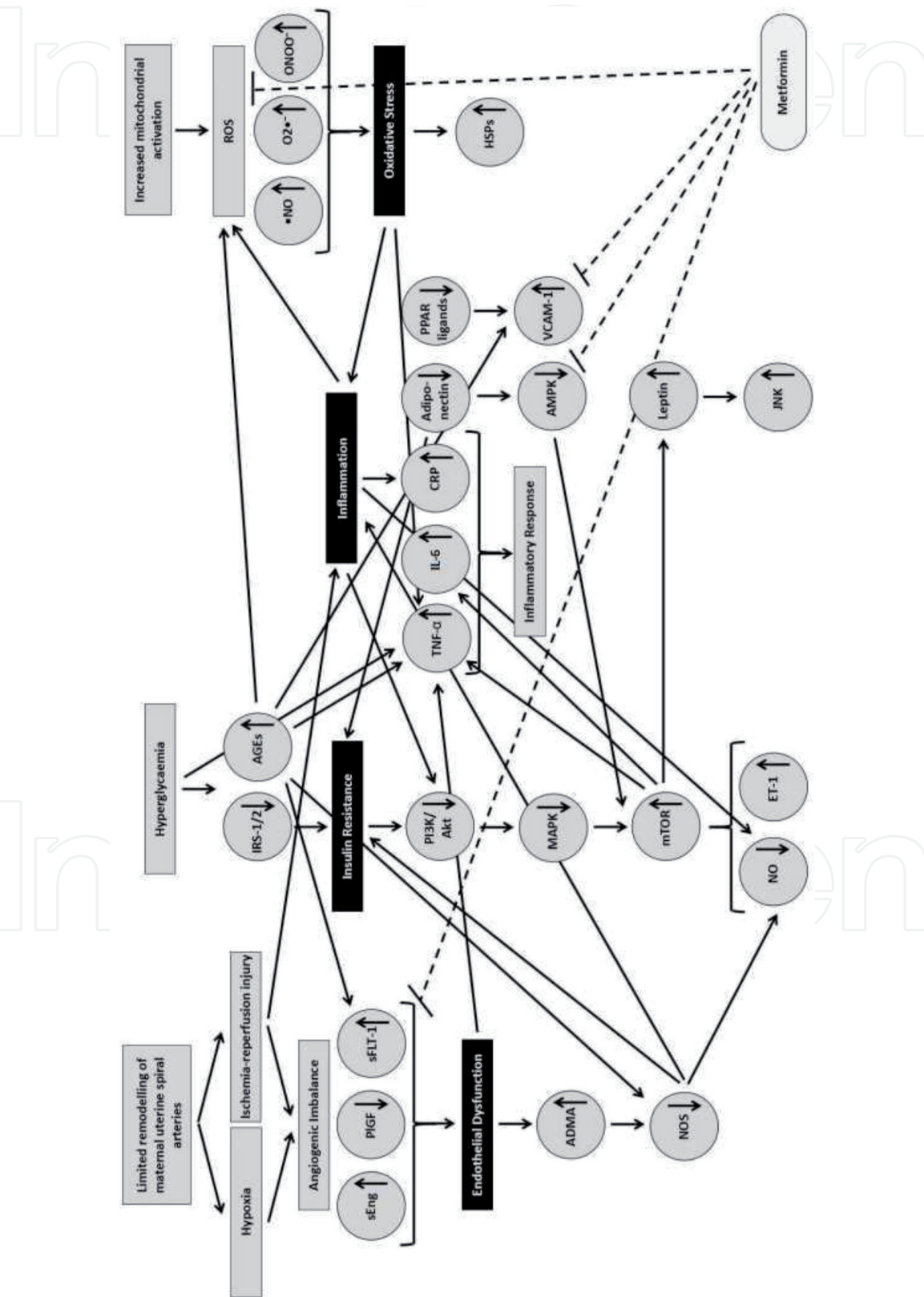


Figure 1.
Overview of the interactions between biochemical pathways common to pre-eclampsia and GDM.

statuses i.e. early- vs. late-onset pre-eclampsia and T1D, pre-existing T2DM, and GDM is required. To achieve this, prospective cohort studies need to be set up in which biochemical data is collected from women at pre-conception, at each trimester during pregnancy and post-partum (ideally with long-term follow-up). Gaining a better understanding of shared and separate pathophysiological pathways would help improve screening and treatment.

Conflict of interest

None.

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References

- [1] Portelli M, Baron B. Clinical presentation of preeclampsia and the diagnostic value of proteins and their methylation products as biomarkers in pregnant women with preeclampsia and their newborns. *Journal of Pregnancy*. 2018;**2018**:1-23
- [2] Nelson DB, Ziadie MS, McIntire DD, Rogers BB, Leveno KJ. Placental pathology suggesting that preeclampsia is more than one disease. *American Journal of Obstetrics and Gynecology*. 2014;**210**(1):66-e1
- [3] Jiواني A, Marseille E, Lohse N, Damm P, Hod M, Kahn JG. Gestational diabetes mellitus: Results from a survey of country prevalence and practices. *The Journal of Maternal-Fetal and Neonatal Medicine*. 2012;**25**(6):600-610
- [4] Buchanan TA, Xiang AH. Gestational diabetes mellitus. *The Journal of Clinical Investigation*. 2005;**115**(3):485-491
- [5] Schneider S, Freerksen N, Röhrig S, Hoeft B, Maul H. Gestational diabetes and preeclampsia—Similar risk factor profiles? *Early Human Development*. 2012;**88**(3):179-184
- [6] Nerenberg KA, Johnson JA, Leung B, Savu A, Ryan EA, Chik CL, et al. Risks of gestational diabetes and preeclampsia over the last decade in a cohort of Alberta women. *Journal of Obstetrics and Gynaecology Canada*. 2013;**35**(11):986-994
- [7] Lisonkova S, Joseph KS. Incidence of preeclampsia: Risk factors and outcomes associated with early-versus late-onset disease. *American Journal of Obstetrics and Gynecology*. 2013;**209**(6):544-5e1
- [8] Weissgerber TL, Mudd LM. Preeclampsia and diabetes. *Current Diabetes Reports*. 2015;**15**(3):9
- [9] Mudd LM, Owe KM, Mottola MF, Pivarnik JM. Health benefits of physical activity during pregnancy: An international perspective. *Medicine and Science in Sports and Exercise*. 2013;**45**(2):268-277
- [10] Mastrogiannis DS, Spiliopoulos M, Mulla W, Homko CJ. Insulin resistance: The possible link between gestational diabetes mellitus and hypertensive disorders of pregnancy. *Current Diabetes Reports*. 2009;**9**(4):296
- [11] Wen SW, Xie RH, Tan H, Walker MC, Smith GN, Retnakaran R. Preeclampsia and gestational diabetes mellitus: Pre-conception origins? *Medical Hypotheses*. 2012;**79**(1):120-125
- [12] Roberts JM, Lain KY. Recent insights into the pathogenesis of pre-eclampsia. *Placenta*. 2002;**23**(5):359-372
- [13] Jauniaux E, Hempstock J, Greenwold N, Burton GJ. Trophoblastic oxidative stress in relation to temporal and regional differences in maternal placental blood flow in normal and abnormal early pregnancies. *The American Journal of Pathology*. 2003;**162**(1):115-125
- [14] Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *The Journal of Clinical Investigation*. 2003;**111**(5):649-658
- [15] Venkatesha S, Toporsian M, Lam C, Hanai JI, Mammoto T, Kim YM, et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nature Medicine*. 2006;**12**(6):642
- [16] Mutter WP, Karumanchi SA. Molecular mechanisms of preeclampsia. *Microvascular Research*. 2008;**75**(1):1-8

- [17] Chaiworapongsa T, Chaemsaitong P, Yeo L, Romero R. Pre-eclampsia part 1: Current understanding of its pathophysiology. *Nature Reviews Nephrology*. 2014;**10**(8):466
- [18] Karumanchi SA. Angiogenic factors in preeclampsia: From diagnosis to therapy. *Hypertension*. 2016;**67**(6):1072-1079
- [19] Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Kai FY, et al. Obstetric anesthesia. *The New England Journal of Medicine*. 2004;**350**:672-683
- [20] Lai J, Larroca SG, Peeva G, Poon LC, Wright D, Nicolaides KH. Competing risks model in screening for preeclampsia by serum placental growth factor and soluble fms-like tyrosine kinase-1 at 30-33 weeks' gestation. *Fetal Diagnosis and Therapy*. 2014;**35**(4):240-248
- [21] Tsiakkas A, Saiid Y, Wright A, Wright D, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 30-34 weeks' gestation. *American Journal of Obstetrics and Gynecology*. 2016;**215**(1):87-e1
- [22] Verlohren S, Stepan H, Dechend R. Angiogenic growth factors in the diagnosis and prediction of pre-eclampsia. *Clinical Science*. 2012;**122**(2):43-52
- [23] Widmer M, Cuesta C, Khan KS, Conde-Agudelo A, Carroli G, Fusey S, et al. Accuracy of angiogenic biomarkers at 20 weeks' gestation in predicting the risk of pre-eclampsia: A WHO multicentre study. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health*. 2015;**5**(4):330-338
- [24] Khalil A, Maiz N, Garcia-Mandujano R, Penco JM, Nicolaides KH. Longitudinal changes in maternal serum placental growth factor and soluble fms-like tyrosine kinase-1 in women at increased risk of pre-eclampsia. *Ultrasound in Obstetrics and Gynecology*. 2016;**47**(3):324-331
- [25] Chaiworapongsa T, Romero R, Whitten AE, Korzeniewski SJ, Chaemsaitong P, Hernandez-Andrade E, et al. The use of angiogenic biomarkers in maternal blood to identify which SGA fetuses will require a preterm delivery and mothers who will develop pre-eclampsia. *The Journal of Maternal-Fetal and Neonatal Medicine*. 2016;**29**(8):1214-1228
- [26] Korzeniewski SJ, Romero R, Chaiworapongsa T, Chaemsaitong P, Kim CJ, Kim YM, et al. Maternal plasma angiogenic index-1 (placental growth factor/soluble vascular endothelial growth factor receptor-1) is a biomarker for the burden of placental lesions consistent with uteroplacental underperfusion: A longitudinal case-cohort study. *American Journal of Obstetrics and Gynecology*. 2016;**214**(5):629-6e1
- [27] Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive value of the sFlt-1: PlGF ratio in women with suspected preeclampsia. *New England Journal of Medicine*. 2016;**374**(1):13-22
- [28] Romero R, Erez O, Hüttemann M, Maymon E, Panaitescu B, Conde-Agudelo A, et al. Metformin, the aspirin of the 21st century: Its role in gestational diabetes mellitus, prevention of preeclampsia and cancer, and the promotion of longevity. *American Journal of Obstetrics and Gynecology*. 2017;**217**(3):282-302
- [29] Portelli M. Measurement of asymmetric dimethyl-arginine (ADMA) and methyl-lysine levels in pregnant women with pre-eclampsia and their newborns [thesis]. Malta: University of Malta; 2018
- [30] Powers RW, Jeyabalan A, Clifton RG, Van Dorsten P, Hauth JC, Klebanoff

- MA, et al. Eunice Kennedy Shriver National Institute of Child Health Human Development Maternal-Fetal Medicine Units Network. Soluble fms-Like tyrosine kinase 1 (sFlt1), endoglin and placental growth factor (PlGF) in preeclampsia among high risk pregnancies. *PloS One*. 2010;**5**(10):e13263
- [31] Rana S, Powe CE, Salahuddin S, Verlohren S, Perschel FH, Levine RJ, et al. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. *Circulation*. 2012;**125**(7):911-919
- [32] Baltajian K, Bajracharya S, Salahuddin S, Berg AH, Geahchan C, Wenger JB, et al. Sequential plasma angiogenic factors levels in women with suspected preeclampsia. *American Journal of Obstetrics and Gynecology*. 2016;**215**(1):89-e1
- [33] Rana S, Karumanchi SA, Levine RJ, Venkatesha S, Rauh-Hain JA, Tamez H, et al. Sequential changes in antiangiogenic factors in early pregnancy and risk of developing preeclampsia. *Hypertension*. 2007;**50**(1):137-142
- [34] Zhao B, Han X, Meng Q, Luo Q. Early second trimester maternal serum markers in the prediction of gestational diabetes mellitus. *Journal of Diabetes Investigation*. 2018;**9**(4):967-974
- [35] Sun X, Qu T, He X, Yang X, Guo N, Mao Y, et al. Screening of differentially expressed proteins from syncytiotrophoblast for severe early-onset preeclampsia in women with gestational diabetes mellitus using tandem mass tag quantitative proteomics. *BMC Pregnancy and Childbirth*. 2018;**18**(1):437
- [36] Bonney EA. Preeclampsia: A view through the danger model. *Journal of Reproductive Immunology*. 2007;**76**(1-2):68-74
- [37] Kim YM, Romero R, Oh SY, Kim CJ, Kilburn BA, Armant DR, et al. Toll-like receptor 4: A potential link between “danger signals,” the innate immune system, and preeclampsia? *American Journal of Obstetrics and Gynecology*. 2005;**193**(3):921-9e1
- [38] Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. *Diabetes Care*. 2007;**30**(Supplement 2):S112-S119
- [39] Villalobos-Labra R, Silva L, Subiabre M, Araos J, Salsoso R, Fuenzalida B, et al. Akt/mTOR role in human foetoplacental vascular insulin resistance in diseases of pregnancy. *Journal of Diabetes Research*. 2017;**2017**:1-13
- [40] Valdés E, Sepúlveda-Martínez Á, Manukián B, Parra-Cordero M. Assessment of pregestational insulin resistance as a risk factor of preeclampsia. *Gynecologic and Obstetric Investigation*. 2014;**77**(2):111-116
- [41] Hauth JC, Clifton RG, Roberts JM, Myatt L, Spong CY, Leveno KJ, et al. Maternal insulin resistance and preeclampsia. *Obstetric Anesthesia Digest*. 2012;**32**(1):42-43
- [42] Alsnes IV, Janszky I, Forman MR, Vatten LJ, Økland I. A population-based study of associations between preeclampsia and later cardiovascular risk factors. *American Journal of Obstetrics and Gynecology*. 2014;**211**(6):657-6e1
- [43] Gunderson EP, Quesenberry CP Jr, Jacobs DR Jr, Feng J, Lewis CE, Sidney S. Longitudinal study of prepregnancy cardiometabolic risk factors and subsequent risk of gestational diabetes mellitus: The CARDIA study. *American Journal of Epidemiology*. 2010;**172**(10):1131-1143

- [44] Reece EA, Leguizamón G, Wiznitzer A. Gestational diabetes: The need for a common ground. *The Lancet*. 2009;**373**(9677):1789-1797
- [45] Yang X, Guo L, Li H, Chen X, Tong X. Analysis of the original causes of placental oxidative stress in normal pregnancy and pre-eclampsia: A hypothesis. *The Journal of Maternal-Fetal and Neonatal Medicine*. 2012;**25**(7):884-888
- [46] Karacay Ö, Sepici-Dincel A, Karcaaltincaba D, Sahin D, Yalvaç S, Akyol M, et al. A quantitative evaluation of total antioxidant status and oxidative stress markers in preeclampsia and gestational diabetic patients in 24-36 weeks of gestation. *Diabetes Research and Clinical Practice*. 2010;**89**(3):231-238
- [47] Burton GJ, Jauniaux E. Oxidative stress. *Best Practice and Research Clinical Obstetrics and Gynaecology*. 2011;**25**(3):287-299
- [48] Lappas M, Hiden U, Desoye G, Froehlich J, Mouzon SH, Jawerbaum A. The role of oxidative stress in the pathophysiology of gestational diabetes mellitus. *Antioxidants and Redox Signaling*. 2011;**15**(12):3061-3100
- [49] Bilodeau JF. Maternal and placental antioxidant response to preeclampsia—impact on vasoactive eicosanoids. *Placenta*. 2014;**35**:S32-S38
- [50] Sánchez-Aranguren LC, Prada CE, Riaño-Medina CE, Lopez M. Endothelial dysfunction and preeclampsia: Role of oxidative stress. *Frontiers in Physiology*. 2014;**5**:372
- [51] Khaing W, Vallibhakara SA, Tantrakul V, Vallibhakara O, Rattanasiri S, McEvoy M, et al. Calcium and vitamin D supplementation for prevention of preeclampsia: A systematic review and network meta-analysis. *Nutrients*. 2017;**9**(10):1141
- [52] Giacco F, Brownlee M. Oxidative stress and diabetic complications. *Circulation Research*. 2010;**107**(9):1058-1070
- [53] Rao R, Sen S, Han B, Ramadoss S, Chaudhuri G. Gestational diabetes, preeclampsia and cytokine release: Similarities and Differences in Endothelial Cell Function. In: *Advances in Fetal and Neonatal Physiology*. New York, NY: Springer; 2014. pp. 69-75
- [54] Rashid G, Benchetrit S, Fishman D, Bernheim J. Effect of advanced glycation end-products on gene expression and synthesis of TNF- α and endothelial nitric oxide synthase by endothelial cells. *Kidney International*. 2004;**66**(3):1099-1106
- [55] Xu B, Ji Y, Yao K, Cao YX, Ferro A. Inhibition of human endothelial cell nitric oxide synthesis by advanced glycation end-products but not glucose: Relevance to diabetes. *Clinical Science*. 2005;**109**(5):439-446
- [56] Yan JY, Jiang LL. Expression of advanced glycation end products in placenta and concentration in maternal and umbilical serum in pre-eclampsia. *Journal of Obstetrics and Gynaecology Research*. 2015;**41**(6):843-849
- [57] Xian N, Chen W, Zhang Y, Li J, Zhang N, Ye Y. Correlation of the expressions of advanced glycation end products and its receptor in serum and placenta with the pathogenesis of preeclampsia. *Zhonghua Fu Chan Ke Za Zhi*. 2015;**50**(7):493-499
- [58] Chen W, Zhang Y, Yue C, Ye Y, Chen P, Peng W, et al. Accumulation of advanced glycation end products involved in inflammation and contributing to severe preeclampsia, in maternal blood, umbilical blood and placental tissues. *Gynecologic and Obstetric Investigation*. 2017;**82**(4):388-397

- [59] Huang QT, Zhang M, Zhong M, Yu YH, Liang WZ, Hang LL, et al. Advanced glycation end products as an upstream molecule triggers ROS-induced sFlt-1 production in extravillous trophoblasts: A novel bridge between oxidative stress and preeclampsia. *Placenta*. 2013;**34**(12):1177-1182
- [60] Genc H, Uzun H, Benian A, Simsek G, Gelisgen R, Madazli R, et al. Evaluation of oxidative stress markers in first trimester for assessment of preeclampsia risk. *Archives of Gynecology and Obstetrics*. 2011;**284**(6):1367-1373
- [61] Arribas L, Almansa I, Miranda M, Muriach M, Romero FJ, Villar VM. Serum malondialdehyde concentration and glutathione peroxidase activity in a longitudinal study of gestational diabetes. *PLoS One*. 2016;**11**(5):e0155353
- [62] Vishnyakova PA, Volodina MA, Tarasova NV, Marey MV, Tsvirkun DV, Vavina OV, et al. Mitochondrial role in adaptive response to stress conditions in preeclampsia. *Scientific Reports*. 2016;**6**:32410
- [63] Shi Z, Long W, Zhao C, Guo X, Shen R, Ding H. Comparative proteomics analysis suggests that placental mitochondria are involved in the development of pre-eclampsia. *PLoS One*. 2013;**8**(5):e64351
- [64] Mihiu D, Razvan C, Malutan A, Mihaela C. Evaluation of maternal systemic inflammatory response in preeclampsia. *Taiwanese Journal of Obstetrics and Gynecology*. 2015;**54**(2):160-166
- [65] Weel IC, Baergen RN, Romão-Veiga M, Borges VT, Ribeiro VR, Witkin SS, et al. Association between placental lesions, cytokines and angiogenic factors in pregnant women with preeclampsia. *PLoS One*. 2016;**11**(6):e0157584
- [66] Wolf M, Sauk J, Shah A, Smirnakis KV, Jimenez-Kimble R, Ecker JL, et al. Inflammation and glucose intolerance: A prospective study of gestational diabetes mellitus. *Diabetes Care*. 2004;**27**(1):21-27
- [67] Kirwan JP, Hauguel-De Mouzon S, Lepercq J, Challier JC, Huston-Presley L, Friedman JE, et al. TNF- α is a predictor of insulin resistance in human pregnancy. *Diabetes*. 2002;**51**(7):2207-2213
- [68] McLachlan KA, O'neal D, Jenkins A, Alford FP. Do adiponectin, TNF α , leptin and CRP relate to insulin resistance in pregnancy? Studies in women with and without gestational diabetes, during and after pregnancy. *Diabetes/ Metabolism Research and Reviews*. 2006;**22**(2):131-138
- [69] Atègbo JM, Grissa O, Yessoufou A, Hichami A, Dramane KL, Moutairou K, et al. Modulation of adipokines and cytokines in gestational diabetes and macrosomia. *The Journal of Clinical Endocrinology and Metabolism*. 2006;**91**(10):4137-4143
- [70] Heitritter SM, Solomon CG, Mitchell GF, Skali-Ounis N, Seely EW. Subclinical inflammation and vascular dysfunction in women with previous gestational diabetes mellitus. *The Journal of Clinical Endocrinology and Metabolism*. 2005;**90**(7):3983-3988
- [71] Miehle K, Stepan H, Fasshauer M. Leptin, adiponectin and other adipokines in gestational diabetes mellitus and pre-eclampsia. *Clinical Endocrinology*. 2012;**76**(1):2-11
- [72] Phaloprakarn C, Tangjitgamol S. Risk assessment for preeclampsia in women with gestational diabetes mellitus. *Journal of Perinatal Medicine*. 2009;**37**(6):617-621
- [73] Knight KM, Pressman EK, Hackney DN, Thornburg LL. Perinatal outcomes

in type 2 diabetic patients compared with non-diabetic patients matched by body mass index. *The Journal of Maternal-Fetal and Neonatal Medicine*. 2012;**25**(6):611-615

[74] Jeyabalan A. Epidemiology of preeclampsia: Impact of obesity. *Nutrition Reviews*. 2013;**71**(suppl_1):S18-S25

[75] Zavalza-Gómez AB, Anaya-Prado R, Rincón-Sánchez AR, Mora-Martínez JM. Adipokines and insulin resistance during pregnancy. *Diabetes Research and Clinical Practice*. 2008;**80**(1):8-15

[76] Ahima RS, Flier JS. Leptin. *Annual Review of Physiology*. 2000;**62**(1):413-437

[77] Hendler I, Blackwell SC, Mehta SH, Whitty JE, Russell E, Sorokin Y, et al. The levels of leptin, adiponectin, and resistin in normal weight, overweight, and obese pregnant women with and without preeclampsia. *American Journal of Obstetrics and Gynecology*. 2005;**193**(3):979-983

[78] Ramsay JE, Jamieson N, Greer IA, Sattar N. Paradoxical elevation in adiponectin concentrations in women with preeclampsia. *Hypertension*. 2003;**42**(5):891-894

[79] Kajantie E, Kaaja R, Ylikorkala O, Andersson S, Laivouri H. Adiponectin concentrations in maternal serum: Elevated in preeclampsia but unrelated to insulin sensitivity. *Journal of the Society for Gynecologic Investigation*. 2005;**12**(6):433-439

[80] Naruse K, Yamasaki M, Umekage H, Sado T, Sakamoto Y, Morikawa H. Peripheral blood concentrations of adiponectin, an adipocyte-specific plasma protein, in normal pregnancy and preeclampsia. *Journal of Reproductive Immunology*. 2005;**65**(1):65-75

[81] Fazeli Daryasari SR, Razavinia F, Tork Tatari F, Pahlevan F, Tehranian N. The role of adiponectin in gestational diabetes mellitus, preeclampsia and obesity during pregnancy: A systematic review. *Iranian Journal of Endocrinology and Metabolism*. 2018;**19**(5):370-383

[82] Chen J, Tan B, Karteris E, Zervou S, Digby J, Hillhouse EW, et al. Secretion of adiponectin by human placenta: Differential modulation of adiponectin and its receptors by cytokines. *Diabetologia*. 2006;**49**(6):1292

[83] Altinova AE, Toruner F, Bozkurt N, Bukan N, Karakoc A, Yetkin I, et al. Circulating concentrations of adiponectin and tumor necrosis factor- α in gestational diabetes mellitus. *Gynecological Endocrinology*. 2007;**23**(3):161-165

[84] Retnakaran R, Connelly PW, Maguire G, Sermer M, Zinman B, Hanley AJ. Decreased high-molecular-weight adiponectin in gestational diabetes: Implications for the pathophysiology of Type 2 diabetes. *Diabetic Medicine*. 2007;**24**(3):245-252

[85] Thagaard IN, Krebs L, Holm JC, Lange T, Larsen T, Christiansen M. Adiponectin and leptin as first trimester markers for gestational diabetes mellitus: A cohort study. *Clinical Chemistry and Laboratory Medicine (CCLM)*. 2017;**55**(11):1805-1812

[86] Retnakaran R, Qi Y, Connelly PW, Sermer M, Hanley AJ, Zinman B. Low adiponectin concentration during pregnancy predicts postpartum insulin resistance, beta cell dysfunction and fasting glycaemia. *Diabetologia*. 2010;**53**(2):268

[87] Haugen F, Ranheim T, Harsem NK, Lips E, Staff AC, Drevon CA. Increased plasma levels of adipokines in preeclampsia: Relationship to placenta and adipose tissue gene expression.

American Journal of Physiology-Endocrinology and Metabolism. 2006;**290**(2):E326-333

[88] Adali E, Yildizhan R, Kolusari A, Kurdoglu M, Bugdayci G, Sahin HG, et al. Increased visfatin and leptin in pregnancies complicated by pre-eclampsia. *The Journal of Maternal-Fetal and Neonatal Medicine*. 2009;**22**(10):873-879

[89] Masuyama H, Segawa T, Sumida Y, Masumoto A, Inoue S, Akahori Y, et al. Different profiles of circulating angiogenic factors and adipocytokines between early-and late-onset pre-eclampsia. *BJOG: An International Journal of Obstetrics and Gynaecology*. 2010;**117**(3):314-320

[90] Anim-Nyame N, Sooranna SR, Steer PJ, Johnson MR. Longitudinal analysis of maternal plasma leptin concentrations during normal pregnancy and pre-eclampsia. *Human Reproduction*. 2000;**15**(9):2033-2036

[91] Chappell LC, Seed PT, Briley A, Kelly FJ, Hunt BJ, Charnock-Jones DS, et al. A longitudinal study of biochemical variables in women at risk of preeclampsia. *American Journal of Obstetrics and Gynecology*. 2002;**187**(1):127-136

[92] Ning Y, Williams MA, Muy-Rivera M, Leisenring WM, Luthy DA. Relationship of maternal plasma leptin and risk of pre-eclampsia: A prospective study. *The Journal of Maternal-Fetal and Neonatal Medicine*. 2004;**15**(3):186-192

[93] Samolis S, Papastefanou I, Panagopoulos P, Galazios G, Kouskoukis A, Maroulis G. Relation between first trimester maternal serum leptin levels and body mass index in normotensive and pre-eclamptic pregnancies—role of leptin as a marker of pre-eclampsia: A prospective case–control study. *Gynecological Endocrinology*. 2010;**26**(5):338-343

[94] Kautzky-Willer A, Pacini G, Tura A, Bieglmayer C, Schneider B, Ludvik B, et al. Increased plasma leptin in gestational diabetes. *Diabetologia*. 2001;**44**(2):164-172

[95] Vitoratos N, Salamalekis E, Kassanos D, Loghis C, Panayotopoulos N, Kouskouni E, et al. Maternal plasma leptin levels and their relationship to insulin and glucose in gestational-onset diabetes. *Gynecologic and Obstetric Investigation*. 2001;**51**(1):17-21

[96] Chen D, Xia G, Xu P, Dong M. Peripartum serum leptin and soluble leptin receptor levels in women with gestational diabetes. *Acta Obstetrica et Gynecologica Scandinavica*. 2010;**89**(12):1595-1599

[97] Hauguel-de Mouzon S, Lepercq J, Catalano P. The known and unknown of leptin in pregnancy. *American Journal of Obstetrics and Gynecology*. 2006;**194**(6):1537-1545

[98] Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nature Reviews Immunology*. 2011;**11**(2):85

[99] Jawerbaum A, Capobianco E. Effects of PPAR activation in the placenta and the fetus: Implications in maternal diabetes. *Placenta*. 2011;**32**:S212-S217

[100] Waite LL, Person EC, Zhou Y, Lim KH, Scanlan TS, Taylor RN. Placental peroxisome proliferator-activated receptor- γ is up-regulated by pregnancy serum. *The Journal of Clinical Endocrinology and Metabolism*. 2000;**85**(10):3808-3814

[101] Waite LL, Louie RE, Taylor RN. Circulating activators of peroxisome proliferator-activated receptors are reduced in preeclamptic pregnancy. *The Journal of Clinical Endocrinology and Metabolism*. 2005;**90**(2):620-626

- [102] McCarthy FP, Drewlo S, English FA, Kingdom J, Johns EJ, Kenny LC, et al. Evidence implicating peroxisome proliferator-activated receptor- γ in the pathogenesis of preeclampsia. *Hypertension*. 2011;**58**(5):882-887
- [103] McCarthy FP, Drewlo S, Kingdom J, Johns EJ, Walsh SK, Kenny LC. Peroxisome proliferator-activated receptor- γ as a potential therapeutic target in the treatment of preeclampsia. *Hypertension*. 2011;**58**(2):280-286
- [104] Holdsworth-Carson SJ, Lim R, Mitton A, Whitehead C, Rice GE, Permezel M, et al. Peroxisome proliferator-activated receptors are altered in pathologies of the human placenta: Gestational diabetes mellitus, intrauterine growth restriction and preeclampsia. *Placenta*. 2010;**31**(3):222-229
- [105] Salzer L, Tenenbaum-Gavish K, Hod M. Metabolic disorder of pregnancy (understanding pathophysiology of diabetes and preeclampsia). *Best Practice and Research Clinical Obstetrics and Gynaecology*. 2015;**29**(3):328-338
- [106] Leavey K, Benton SJ, Grynspan D, Kingdom JC, Bainbridge SA, Cox BJ. Unsupervised placental gene expression profiling identifies clinically relevant subclasses of human preeclampsia. *Hypertension*. 2016;**68**(1):137-147
- [107] Lowe WL, Scholtens DM, Sandler V, Hayes MG. Genetics of gestational diabetes mellitus and maternal metabolism. *Current Diabetes Reports*. 2016;**16**(2):15
- [108] Wu L, Cui L, Tam WH, Ma RC, Wang CC. Genetic variants associated with gestational diabetes mellitus: A meta-analysis and subgroup analysis. *Scientific Reports*. 2016;**6**:30539
- [109] Enquobahrie DA, Williams MA, Qiu C, Meller M, Sorensen TK. Global placental gene expression in gestational diabetes mellitus. *American Journal of Obstetrics and Gynecology*. 2009;**200**(2):206-2e1
- [110] Cutfield WS, Hofman PL, Mitchell M, Morison IM. Could epigenetics play a role in the developmental origins of health and disease? *Pediatric Research*. 2007;**61**(5 Part 2):68R
- [111] Schroeder DI, Jayashankar K, Douglas KC, Thirkill TL, York D, Dickinson PJ, et al. Early developmental and evolutionary origins of gene body DNA methylation patterns in mammalian placentas. *PLoS Genetics*. 2015;**11**(8):e1005442
- [112] Jia RZ, Zhang X, Hu P, Liu XM, Hua XD, Wang X, et al. Screening for differential methylation status in human placenta in preeclampsia using a CpG island plus promoter microarray. *International Journal of Molecular Medicine*. 2012;**30**(1):133-141
- [113] Ruchat SM, Houde AA, Voisin G, St-Pierre J, Perron P, Baillargeon JP, et al. Gestational diabetes mellitus epigenetically affects genes predominantly involved in metabolic diseases. *Epigenetics*. 2013;**8**(9):935-943
- [114] Blair JD, Yuen RK, Lim BK, McFadden DE, von Dadelszen P, Robinson WP. Widespread DNA hypomethylation at gene enhancer regions in placentas associated with early-onset pre-eclampsia. *Molecular Human Reproduction*. 2013;**19**(10):697-708
- [115] Anton L, Brown AG, Bartolomei MS, Elovitz MA. Differential methylation of genes associated with cell adhesion in preeclamptic placentas. *PLoS One*. 2014;**9**(6):e100148
- [116] Chu T, Bunce K, Shaw P, Shridhar V, Althouse A, Hubel

- C, et al. Comprehensive analysis of preeclampsia-associated DNA methylation in the placenta. *PLoS One*. 2014;**9**(9):e107318
- [117] Liu L, Zhang X, Rong C, Rui C, Ji H, Qian YJ, et al. Distinct DNA methylomes of human placentas between pre-eclampsia and gestational diabetes mellitus. *Cellular Physiology and Biochemistry*. 2014;**34**(6):1877-1889
- [118] Petropoulos S, Guillemin C, Ergaz Z, Dimov S, Suderman M, Weinstein-Fudim L, et al. Gestational diabetes alters offspring DNA methylation profiles in human and rat: Identification of key pathways involved in endocrine system disorders, insulin signaling, diabetes signaling, and ILK signaling. *Endocrinology*. 2015;**156**(6):2222-2238
- [119] Finer S, Mathews C, Lowe R, Smart M, Hillman S, Foo L, et al. Maternal gestational diabetes is associated with genome-wide DNA methylation variation in placenta and cord blood of exposed offspring. *Human Molecular Genetics*. 2015;**24**(11):3021-3029
- [120] Binder AM, LaRocca J, Lesseur C, Marsit CJ, Michels KB. Epigenome-wide and transcriptome-wide analyses reveal gestational diabetes is associated with alterations in the human leukocyte antigen complex. *Clinical Epigenetics*. 2015;**7**(1):79
- [121] Nomura Y, Lambertini L, Rialdi A, Lee M, Mystal EY, Grabie M, et al. Global methylation in the placenta and umbilical cord blood from pregnancies with maternal gestational diabetes, preeclampsia, and obesity. *Reproductive Sciences*. 2014;**21**(1):131-137
- [122] Reichetzeder C, Putra SD, Pfab T, Slowinski T, Neuber C, Kleuser B, et al. Increased global placental DNA methylation levels are associated with gestational diabetes. *Clinical Epigenetics*. 2016;**8**(1):82
- [123] Williams KT, Schalinske KL. Tissue-specific alterations of methyl group metabolism with DNA hypermethylation in the Zucker (type 2) diabetic fatty rat. *Diabetes/ Metabolism Research and Reviews*. 2012;**28**(2):123-131
- [124] Rani V, Deep G, Singh RK, Palle K, Yadav UC. Oxidative stress and metabolic disorders: Pathogenesis and therapeutic strategies. *Life Sciences*. 2016;**148**:183-193
- [125] Zhong J, Xu C, Reece EA, Yang P. The green tea polyphenol EGCG alleviates maternal diabetes-induced neural tube defects by inhibiting DNA hypermethylation. *American Journal of Obstetrics and Gynecology*. 2016;**215**(3):368-3e1
- [126] Morales-Prieto DM, Chaiwangyen W, Ospina-Prieto S, Schneider U, Herrmann J, Gruhn B, et al. MicroRNA expression profiles of trophoblastic cells. *Placenta*. 2012;**33**(9):725-734
- [127] Chim SS, Shing TK, Hung EC, Leung TY, Lau TK, Chiu RW, et al. Detection and characterization of placental microRNAs in maternal plasma. *Clinical Chemistry*. 2008;**54**(3):482-490
- [128] Li H, Ge Q, Guo L, Lu Z. Maternal plasma miRNAs expression in preeclamptic pregnancies. *BioMed Research International*. 2013;**2013**:1-9
- [129] Pineles BL, Romero R, Montenegro D, Tarca AL, Han YM, Kim YM, et al. Distinct subsets of microRNAs are expressed differentially in the human placentas of patients with preeclampsia. *American Journal of Obstetrics and Gynecology*. 2007;**196**(3):261-2e1
- [130] Zhu XM, Han T, Sargent IL, Yin GW, Yao YQ. Differential expression profile of microRNAs in human placentas from preeclamptic pregnancies vs normal pregnancies.

American Journal of Obstetrics and Gynecology. 2009;**200**(6):661-6e1

Journal of Gynecology and Obstetrics. 2015;**130**(1):49-53

[131] Hu Y, Li P, Hao S, Liu L, Zhao J, Hou Y. Differential expression of microRNAs in the placenta of Chinese patients with severe pre-eclampsia. *Clinical Chemistry and Laboratory Medicine*. 2009;**47**(8):923-929

[138] Li J, Song L, Zhou L, Wu J, Sheng C, Chen H, et al. A microRNA signature in gestational diabetes mellitus associated with risk of macrosomia. *Cellular Physiology and Biochemistry*. 2015;**37**(1):243-252

[132] Enquobahrie DA, Abetew DF, Sorensen TK, Willoughby D, Chidambaram K, Williams MA. Placental microRNA expression in pregnancies complicated by preeclampsia. *American Journal of Obstetrics and Gynecology*. 2011;**204**(2):178-e12

[139] Tryggestad JB, Vishwanath A, Jiang S, Mallappa A, Teague AM, Takahashi Y, et al. Influence of gestational diabetes mellitus on human umbilical vein endothelial cell miRNA. *Clinical Science*. 2016;**130**(21):1955-1967

[133] Muralimanoharan S, Maloyan A, Mele J, Guo C, Myatt LG, Myatt L. MIR-210 modulates mitochondrial respiration in placenta with preeclampsia. *Placenta*. 2012;**33**(10):816-823

[140] Collares CV, Evangelista AF, Xavier DJ, Rassi DM, Arns T, Foss-Freitas MC, et al. Identifying common and specific microRNAs expressed in peripheral blood mononuclear cell of type 1, type 2, and gestational diabetes mellitus patients. *BMC Research Notes*. 2013;**6**(1):491

[134] Betoni JS, Derr K, Pahl MC, Rogers L, Muller CL, Packard RE, et al. MicroRNA analysis in placentas from patients with preeclampsia: Comparison of new and published results. *Hypertension in Pregnancy*. 2013;**32**(4):321-339

[141] Floris I, Descamps B, Vardeu A, Mitić T, Posadino AM, Shantikumar S, et al. Gestational diabetes mellitus impairs fetal endothelial cell functions through a mechanism involving microRNA-101 and histone methyltransferase enhancer of zester homolog-2. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2015;**35**(3):664-674

[135] Zhang Y, Fei M, Xue G, Zhou Q, Jia Y, Li L, et al. Elevated levels of hypoxia-inducible microRNA-210 in pre-eclampsia: New insights into molecular mechanisms for the disease. *Journal of Cellular and Molecular Medicine*. 2012;**16**(2):249-259

[142] Nanovskaya TN, Nekhayeva IA, Patrikeeva SL, Hankins GD, Ahmed MS. Transfer of metformin across the dually perfused human placental lobule. *American Journal of Obstetrics and Gynecology*. 2006;**195**(4):1081-1085

[136] Zhao C, Dong J, Jiang T, Shi Z, Yu B, Zhu Y, et al. Early second-trimester serum miRNA profiling predicts gestational diabetes mellitus. *PLoS One*. 2011;**6**(8):e23925

[143] Cassina M, Dona M, Di Gianantonio E, Litta P, Clementi M. First-trimester exposure to metformin and risk of birth defects: A systematic review and meta-analysis. *Human Reproduction Update*. 2014;**20**(5):656-669

[137] Zhu Y, Tian F, Li H, Zhou Y, Lu J, Ge Q. Profiling maternal plasma microRNA expression in early pregnancy to predict gestational diabetes mellitus. *International*

[144] Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: From

mechanisms of action to therapies. *Cell Metabolism*. 2014;**20**(6):953-966

[145] Ainuddin J, Karim N, Hasan AA, Naqvi SA. Metformin versus insulin treatment in gestational diabetes in pregnancy in a developing country. A randomized control trial. *Diabetes Research and Clinical Practice*. 2015;**107**(2):290-299

[146] Butalia S, Gutierrez L, Lodha A, Aitken E, Zakariasen A, Donovan L. Short-and long-term outcomes of metformin compared with insulin alone in pregnancy: A systematic review and meta-analysis. *Diabetic Medicine*. 2017;**34**(1):27-36

[147] Alqudah A, McKinley MC, McNally R, Graham U, Watson CJ, Lyons TJ, et al. Risk of pre-eclampsia in women taking metformin: A systematic review and meta-analysis. *Diabetic Medicine*. 2018;**35**(2):160-172

[148] Brownfoot FC, Hastie R, Hannan NJ, Cannon P, Tuohey L, Parry LJ, et al. Metformin as a prevention and treatment for preeclampsia: Effects on soluble fms-like tyrosine kinase 1 and soluble endoglin secretion and endothelial dysfunction. *American Journal of Obstetrics and Gynecology*. 2016;**214**(3):356-3e1